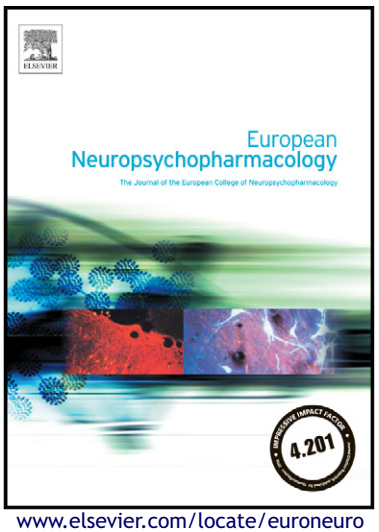

Hallucinogen persisting perception disorder and the serotonergic system: A comprehensive review including new MDMA-related clinical cases

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Hallucinogen persisting perception disorder and the serotonergic system: A comprehensive review including new MDMA-related clinical cases.

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Short title: HPPD, MDMA and the serotonergic system.

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Abstract:

Hallucinogen persisting perception disorder (HPPD) is a drug-induced condition associated with inaccurate visual representations. Since the underlying mechanism(s) are largely unknown, this review aims to uncover aspects underlying its etiology. Available evidence on HPPD and drug-related altered visual processing was reviewed and the majority of HPPD cases were attributed to drugs with agonistic effects on serotonergic 5-HT_{2A} receptors. Moreover, we present 31 new HPPD cases that link HPPD to the use of ecstasy (MDMA), which is known to reverse serotonin reuptake and acts as agonist on 5-HT_{2A} receptors. The available evidence suggests that HPPD symptoms may be a result from a misbalance of inhibitory-excitatory activity in low-level visual processing and GABA-releasing inhibitory interneurons may be involved. However, high co-morbidities with anxiety, attention problems and derealization symptoms add complexity to the etiology of HPPD. Also, other perceptual disorders that show similarity to HPPD cannot be ruled out in presentations to clinical treatment. Taken together, evidence is still sparse, though low-level visual processing may play an important role. A novel finding of this review study, evidenced by our new cases, is that ecstasy (MDMA) use may also induce symptoms of HPPD.

Keywords: HPPD, hallucinogen, LSD, MDMA, ecstasy, 5-HT_{2A} receptor

1. Introduction

The use of hallucinogenic drugs, like psilocybin and LSD, can induce a variety of powerful perceptual symptoms, including altered shapes and colors, trails of moving objects, kaleidoscopic images, and less frequently, auditory and olfactory hallucinations (Dubois and VanRullen, 2011; Kleinman et al., 1977). Hallucinogenic drugs are considered relatively harmless to self and others compared to alcohol, heroin, (crack) cocaine, and tobacco (Nutt et al., 2007; Nutt et al., 2010). However, the main risk of hallucinogenic drugs is the impairment of mental functioning and psychosis (Geyer and Vollenweider, 2008). A special case of impairment of mental functioning appears to occur in a subgroup of users that suffer from persistent perceptual symptoms long after the drug has been used (Abraham and Aldridge, 1993). This is often described by users as a persistent drug trip. These cases of persistent drug trips have also increasingly presented themselves at the level of psychiatric treatment and symptoms have therefore been included in the DSM IV-TR as 'Hallucinogen Persisting Perception Disorder (HPPD)', also colloquially indicated as 'flashbacks' (APA. DSM-IV., 2000).

Estimates of the prevalence of use of hallucinogenic drugs vary greatly between countries. For instance, in Europe, estimates for lifetime LSD use range from 1.3% (Denmark) to 5.3% (England and Wales) (EMCDDA, 2011). In subgroups of the population, these numbers can be much higher, amounting to 6.4% for LSD, 24.7% for magic mushrooms (main psychoactive constituent psilocybin) and 41.6% for ecstasy (van der Poel et al., 2010). Though these numbers should be interpreted with caution and population prevalence figures are impossible to ascertain with drugs that enjoy a small popularity, many suggest that there is a consistent number of experimental users exposed to hallucinogenic substances through time (McCambridge et al., 2007; Ramo et al., 2010).

It is virtually impossible to indicate to which extent hallucinogenic drug use may actually lead to a classification of HPPD (Halpern and Pope, 2003) and it is largely unknown what types of hallucinogenic drugs are implicated in HPPD or how the mechanism of action of these hallucinogenic drugs relates to the visual component of the disorder. We therefore critically

reviewed the existing HPPD literature and provide 31 new cases that implicate the use of ecstasy (MDMA), alongside classical hallucinogens, as a risk factor for developing HPPD.

2. The psychiatric definition of HPPD

An individual's perception can be severely altered when under the influence of the acute effects of certain drugs. These effects slowly wear off as metabolism and excretion gradually clear the drug from the body. In some individuals, however, these perceptual changes do not seem to fade after the drug(s) has been cleared from the body. These individuals may undergo prolonged changes in their normal perception that persist for weeks to indefinite time after exposure (Abraham and Duffy, 1996; Lerner et al., 2000). Original cases, mostly in relation to LSD, date back to the 1950's and 1960's (Asher, 1971; Cooper, 1955; Smart and Bateman, 1967). Initially, the symptoms were included as a distinct disorder in the *Diagnostic and statistical manual of mental disorders* (DSM III-R) in 1986 as 'posthallucinogen perception disorder' (Halpern and Pope, 2003). After some adaptations over the years the disorder is included in the DSM IV-TR at present as 'Hallucinogen persisting perception disorder (flashbacks)' with the following criteria (APA. DSM-IV., 2000):

A. *The re-experiencing, following the use of a hallucinogen, of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen (e.g., geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes of color, intensified colors, trails of images of moving objects, positive afterimages, halos around objects, macropsia, and micropsia).*
B. *The symptoms in Criterion A cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.*
C. *The symptoms are not due to a general medical condition (e.g., anatomical lesions and infections of the brain, visual epilepsies) and are not better accounted for by another mental disorder (e.g., delirium, dementia, schizophrenia) or hypnopompic hallucinations.*

According to the DSM IV-TR, the symptoms typically occur in episodes and can be triggered by entering into a dark environment, acute intoxication with alcohol or marihuana, anxiety, fatigue, different stressors, or by thinking of them (self-induced) (Abraham, 1983;

APA. DSM-IV., 2000). HPPD can also occur in the form of constant visual distortions without a distinct trigger (Abraham and Duffy, 2001). Although the DSM IV-TR title is HPPD ('flashbacks'), flashbacks are often short-term, spontaneous and reversible, whereas HPPD by definition is a long-lasting, distressing, recurrent condition (Lerner et al., 2002). Symptoms reported by HPPD patients are generally visual, but auditory symptoms may also occur. When diagnosing HPPD it is important to rule out other conditions with altered perception, such as visual epilepsies, migraine, delirium, dementia, schizophrenia, and hypnopompic hallucinations (APA. DSM-IV., 2000). Notably, HPPD patients are aware of the fact that their hallucinations are not real (APA. DSM-IV., 2000). Another defining characteristic of HPPD patients compared to patients with other hallucinatory mental disorders is that they often have extensive drug histories and related symptomatology.

3. The epidemiology of HPPD

Epidemiological information about HPPD is scarce. Persons suffering from HPPD appear to be predominantly male and develop HPPD symptoms during adolescence (Abraham, 1983; Abraham and Duffy, 2001). The prevalence of HPPD is probably low, but hard to estimate because hallucinogenic drug use in the general population seems to be limited and there may be reluctance to seek treatment because of fear of prosecution, guilt and/or stigmatization (Appel et al., 2004).

There are several studies on long-lasting perceptual symptoms dating from before the condition was first mentioned in the DSM III-R as post-hallucinogen perception disorder (Halpern and Pope, 2003). However, many of these studies did not supply sufficient information to determine whether the reported 'flashbacks' were cases of HPPD. Furthermore, a vast amount of these old studies included patients with a history of schizophrenia and other serious mental disorders.

In 2003, a thorough analysis of the literature on HPPD and flashbacks was published (Halpern and Pope, 2003). According to this review, the prevalence of HPPD-like symptoms among drug users ranges from <5% in subjects receiving therapeutic LSD (McGlothlin and Arnold, 1971) to ~50% in multi-substance abusers (Holsten, 1976). In a more recent web-based questionnaire 61% of the respondents (with extensive drugs histories) reported at least one type of recurring visual experience and 24% reported this on a constant or near-constant basis. However, indication for the occurrence of HPPD seemed limited as treatment was considered by only 4.2% of the subjects because symptoms had caused substantial disabilities in daily functioning (Baggott et al., 2011). In an additional web-based questionnaire comparable prevalence rates were found, with 40% of the respondents reporting persistent moderate or severe visual changes and a possible 1-11% of the participants fulfilling DSM IV-TR criteria A and B (persistent visual changes and incapacitated) (Carhart-Harris and Nutt, 2010).

Persistent visual symptoms were encountered less when drugs were administered in controlled research or therapeutic settings. This lower incidence has been ascribed to careful

preparation, screening, supervision, aftercare, and the use of pharmaceutical quality drugs (Halpern and Pope, 2003). Furthermore, the studies including lay drug users consisted mostly of multi-drug users, and so multidrug use may very well increase the chance of developing HPPD. Recent web-based studies suggest that the occurrence of HPPD is suspected within a small proportion of these users, although the reliability of web-based questionnaires is difficult to measure (Carhart-Harris and Nutt, 2010; Baggott et al., 2011).

4. The visual system and HPPD

4.1 The visual system

Photoreceptors of the retina decrease their glutamate release when light shines on the retina, thereby translating light into a neurotransmitter signal. Groups of photoreceptors are connected to bipolar cells, which in turn signal to ganglion cells that project to the brain with their axons bundled in the optic nerve. Approximately 80% of the optic nerve fibers project to a portion of the thalamus called the lateral geniculate nucleus (LGN) (Blake and Sekuler, 2006). The thalamus receives visual, auditory, gustatory, and sensory information and may be an important region in the subjective experience induced by hallucinogens (Nichols, 2004). Cells of the LGN have ON- and OFF-centered receptive fields similar to retinal ganglion cells, but differ from retinal cells in that the surround of their fields exert a stronger inhibitory effect on the center. This results in an accentuation of contrasts that is stronger in cells of the LGN than in retinal ganglion cells, positioning the LGN as a crucial area of registration of contrasts in the environment (Blake and Sekuler, 2006).

From the LGN visual information is sent to the primary visual cortex (V1), which is located in the posterior pole of the occipital cortex. Feed forward driven activity in V1 is greatly reduced by AMPA receptor antagonism, which implies that glutamate plays an important role in transmitting the excitatory signal from the LGN to V1 (Sato et al., 1999; Self et al., 2012). In contrast to the LGN, the neurons in V1 also respond to more complex stimuli involving orientation and motion. From V1, the visual pathway ascends through the visual cortex to higher brain areas that contain neurons specific for still more complex stimuli, such as specific types of motion, or typical objects like faces. Higher brain areas in their turn also provide feedback to lower areas, making the visual system a complex structure (Blake and Sekuler, 2006).

4.2 HPPD symptoms and the visual system

HPPD is a perceptual disorder and some of the previously mentioned visual symptoms have received scientific attention.

Geometric hallucinations are patterns that are generally perceived with both eyes and move, while maintaining their relative position in the visual field (see *figure 1*) (Bressloff et al., 2002). However, in the vast majority of HPPD patients the geometric patterns do not track with eye movement, as opposed to vitreous floaters for example (Abraham, personal communication). This suggests that these geometric hallucinations likely originate in the CNS and not at the level of the eye itself. For example, patients with HPPD have abnormalities in sensory evoked potentials measureable by scalp electrodes (Abraham and Duffy, 1996, 2001).

Additionally, the prolonged nature of these hallucinations separates the effects seen in HPPD from effects resulting from basic changes at the level of the eye, like pressure phosphenes (Billock and Tsou, 2012). These are commonly referred to as elementary hallucinations and there is no mentioning of these in relation to conditions with chronic intraocular hypertension, such as glaucoma. Theoretical studies have suggested that the neurophysiology of V1 is suitable for the generation of geometric hallucinations (Bressloff et al., 2002).

Place Figure 1 here

Trailing (see *figure 2*) is another visual phenomenon that can be experienced under the acute influence of hallucinogenic drugs and that may persist in patients with HPPD. Trailing usually affects only few moving objects at a time, making it unlikely that the symptoms originate at the level of the eyes but again implying a cause in the brain (Dubois and VanRullen, 2011). Though this finding is based on a small sample size (Dubois, personal communication), computational research also suggests the symptoms of trailing could originate in the brain (V1 of the primary visual cortex), and that they may be the result from activity in a population of neurons that remains active after the stimulus input is no longer

present (Kilpatrick and Bard Ermentrout, 2012). It also differs from akinetopsia, a rare condition whereby patients are unable to visually perceive motion at all (Zeki, 1991).

Place Figure 2 here

Somewhat similar to trailing, afterimages are images that persist in vision after the stimulus has disappeared (see *Figure 3*) (Dubois and VanRullen, 2011). Positive afterimages are most frequently observed by HPPD patients and have the same color composition as the original stimulus. Negative afterimages, which have inverted colors, are less frequently observed in HPPD patients (Abraham, 1983). Positive afterimages have been linked to posterior visual pathway lesions and the effects of medications such as trazodone and clomiphene citrate (Hughes and Lessell, 1990; Purvin, 1995; Ritsema and Murphy, 2007). Negative afterimages are thought to result from desensitization of photoreceptors in the retina of the eye (Brindley, 1962; Ritschel and Eisemann, 2012), but may also arise through a brain mechanism that remains to be elucidated. Taken together, these findings could point to an origin for HPPD complaints in the brain rather than the eye.

Place Figure 3 here

There is also evidence suggesting HPPD symptoms are more likely the result of a disturbance in lower levels of the visual pathway of the brain. Kilpatrick and Bard Ermentrout (2012) reason that the finding that HPPD patients rarely believe their hallucinations indicates that higher brain regions are not involved. The limited information available on some of the symptoms experienced by HPPD patients points in the direction of the primary visual cortex. However, since auditory and sensory symptoms are also present in some individuals, the thalamus, in particular the lateral geniculate nucleus (LGN), deserves consideration. In addition, it is important to keep in mind that multiple areas may be involved and that a role for higher brain regions is not excluded.

5. Hallucinogenic substances, the serotonergic system, and HPPD

5.1 Pharmacodynamics of hallucinogens

A key feature of many hallucinogens is that they affect serotonergic neurotransmission to some extent. For instance, LSD acts as an agonist at 5-HT_{1A} auto-receptors, thereby targeting neurons in the prefrontal cortex (PFC), locus coeruleus (LC), and the raphe nuclei. As such, serotonin release may be affected in the many brain areas that are innervated by serotonin-releasing axons from the raphe nuclei (Passie et al., 2008). Like LSD, psilocin (the active metabolite of psilocybin) interacts with several serotonin receptor subtypes, including 5-HT_{1A} (Passie et al., 2002b), and may inhibit firing of raphe nuclei neurons. However, the effect on firing was not essential for the hallucinogenic effects (Nichols, 2004), suggesting that the (partial) agonistic effects at 5-HT receptors are more important than the decrease in 5-HT brain levels. In line with this, it appears that the psychoactive potency of hallucinogens correlates strongly with their affinity for 5-HT_2 receptors (Glennon et al., 1984; Titeler et al., 1988). This holds for ergotamines (e.g. LSD), tryptamines (e.g. psilocybin, DMT) and for hallucinogens of the phenetylamine group (e.g., mescaline, 2C-B, 2C-I, 2C-E). Although hallucinogens generally have a similar affinity for both the 5-HT_{2A} and the 5-HT_{2C} receptor, further research indicated that the specific psychoactive effects of hallucinogens are primarily the result of (partial) agonism at 5-HT_{2A} (Nichols, 2004). Since hallucinogenic effects depend on activity at the 5-HT_{2A} receptor, and because some of the HPPD symptoms are reminiscent of those experienced under acute influence, it may be anticipated that this receptor is involved in the etiology of HPPD.

5.2 Prescription drugs

Some serotonergic prescription drugs induced altered perceptions that bear a degree of similarity to HPPD-like symptoms. Experiences of visual trailing have occurred in psychiatric patients receiving 5-HT_2 antagonist medications (Dubois and VanRullen, 2011), whereas a worsening of existing HPPD symptoms was experienced by HPPD patients receiving the 5-HT_{2A} antagonist risperidone, and 5-HT_2 antagonist phenothiazines (Abraham, 1983;

Abraham and Mamen, 1996; Morehead, 1997). Worsening of the condition also occurred in patients with HPPD-like symptoms after treatment with SSRI's (Markel et al., 1994). Therefore, the 5-HT_{2A} receptor, and serotonergic neurotransmission in general, may be involved in the etiology of HPPD.

5.3 MDMA

Though MDMA is generally not considered a hallucinogen and hallucinations are not frequently reported in studies with human subjects on MDMA (Vollenweider et al., 1998; Winter, 2009), hallucinations and more subtle visual effects, such as color changes have been reported as an effect of pills that were found to contain exclusively MDMA (Brunt et al., 2012; Liechti et al., 2000; Peiro et al., 2012). Moreover, discrimination tests in rats do indicate similarities in effects between serotonergic hallucinogens and MDMA (Gatch et al., 2009; Goodwin and Baker, 2000) and there is at least one existing case report of persisting perceptual symptoms linked to MDMA ('ecstasy') (Passie et al., 2002a). MDMA acts as a potent releaser and reuptake inhibitor of 5-HT, dopamine and noradrenaline. It has highest affinity for the serotonin transporter (SERT) and facilitates release of 5-HT from the presynaptic neuron by reversing the transporter (Rietjens et al., 2012). Blocking of this transporter with citalopram causes a reduction in the experienced visual effects (Liechti et al., 2000). Interestingly, MDMA also has moderate affinity as an agonist at the 5-HT_{2A} receptor (Rietjens et al., 2012). In support of a central role for serotonergic neurotransmission in HPPD, we present a series of new cases (*Table 1*), not previously described in literature, many of which involving MDMA as the suspected causative agent.

5.4 New cases

Our HPPD cases were obtained from a psychiatric consultancy service at an addiction care center in the Netherlands. The majority of individuals, approximately 80%, that applied for consultation found out about it through the internet. Generally, individuals search for their symptoms with the use of a search engine and find the website of Brijder Addiction Care

(www.drugsinfoteam.nl), which shows a description of HPPD symptoms and other conditions that may develop as a result of (hallucinogenic) drug use. Others may be redirected to the consulting hour by their general practitioner or mental health care professional.

Individuals were interviewed with a standard checklist that covered social situation and somatic, motoric, urogentical, gastrointestinal, perceptual, infectious, cardiovascular, and psychiatric symptoms. The symptom checklist was developed over the four years during which intakes took place and was expanded in response to patients' self-reported symptoms. Until October 2012 there were 104 intakes of which 31 unpublished cases were selected that may meet the criteria for HPPD (Table 1). The other cases included other disturbances, such as auditory/ other hallucinations or visual symptoms that were not of a recurring nature. All cases were diagnosed by a psychiatric physician in addiction medicine according to DSM IV-TR criteria.

The included cases reported at least 2 different visual phenomena with a minimum of one episode of disturbed perception every week; the main selection criterion was therefore the individual's re-experience of visual symptoms. Patients were asked if they frequently suffered from headaches and if they had a history of epilepsy or migraine, but no extensive neurological investigations were performed. One individual was excluded because she had a history of headaches that may have been indicative of migraine.

The included cases display visual symptoms with especially high prevalence rates of symptoms such as visual snow, afterimages, flashes, illusory movement, and increased observation of floaters. Floaters or 'mouches volantes', being deposits in the vitreous humor of the eye, are also observed by healthy individuals, but do not generally cause disability since they are eventually filtered out from visual perception. Since five patients who were investigated by an ophthalmologist on their own initiative showed no abnormalities in the eye, it seems that the increased observation of floaters is related to some other underlying pathology. An additional eight patients were investigated by a neurologist, which did not reveal any abnormalities.

Besides recurring visual symptoms, a large group of patients also reported other perceptual symptoms, like auditory and sensory symptoms. A relatively large subgroup (45%) reported peculiar sensations in the head such as pressure, clicks, dryness or 'a shrinking brain'. Striking also, is the co-occurrence of derealization and depersonalization symptoms (39% and 32%), which are characterized by the external environment and own body coming across as unreal or not one's own. Most frequent is the comorbidity with anxiety and panic. Approximately two thirds of the patients (71%) reported to have experienced anxiety or panic in the weeks before or following the use of drugs.

Most of our cases attributed the development of their symptoms to the intake of ecstasy (MDMA). It is not always clear from these cases, however, if the symptoms can be attributed to ecstasy or whether the condition has developed as a result of combinational drug use or other factors. There were some individuals that reported symptoms directly after a single drug exposure, whereas others reported symptoms only after a period of extensive drug use. Interestingly, serotonergic drugs stand out in most of the cases that we report here. This is in good agreement with web-based questionnaires that report respectively 80% and 78% involvement of serotonergic drugs in those individuals that report a causative drug association (Baggott et al., 2011; Carhart-Harris and Nutt, 2010).

Place *Table 1* here

5.5 Other possible causes

An issue of concern for the visual symptomatology of HPPD is the fact that other conditions may actually be causing these visual symptoms, making it difficult to ascertain whether these symptoms are unique to hallucinogenic drug users. With regard to research on comparable enduring perceptual disturbances, there are some disorders that could be implicated.

For instance, migraine with aura is characterized by a prodromal phase during which visual, sensory, motor, and language deficits, usually lasting shorter than 1 hour, precede a migraine headache (Russell and Olesen, 1996; Brigo et al., 2013). There may also be some

mechanistic links between HPPD and migraine with aura since there is large structural similarity between migraine medication (triptans, ergotamines) and hallucinogens (tryptamines, LSD) and because psilocybin can dose-dependently induce headaches that are reminiscent of migraine headaches (Wilkinson, 2004; Johnson et al., 2012). However, headaches or a familial history of migraine were not mentioned by our MDMA cases. In addition, typical visual phenomena of migraine with aura are the fortification spectra with a zigzagged line gradually proceeding across the visual field and scotoma (Russell and Olesen, 1996). These phenomena were completely absent in our sample. Moreover, the visual hallucinations associated with migraine with aura are usually of a temporary nature and resolve after the migraine seizure.

Patients that suffer from persistent migraine aura (PMA) report constant visual symptoms such as visual snow and flashes (Liu et al., 1995), which are also prominent in our cases. However, according to Chen et al. (2011) there are only around 40 cases known cases of PMA worldwide and the cases described suffer from more than 10 headache episodes on a monthly basis. Thus, these documented cases of PMA are clearly distinct from our cases in their overt expression of headaches.

Another well-known example involves visual hallucinations and epileptic auras that occur in patients suffering from occipital or temporal-occipital lobe epilepsy (Wilkinson, 2004; Elliott et al., 2009). Occipital lobe epilepsies may involve visual experiences that include the observation of colored round-shaped figures that bare some similarity to HPPD symptoms, but often progress into clonic tonic seizures and headaches (Panayiotopoulos, 1999). In the case of temporal lobe abnormalities, the visual hallucinations are often of a more complex nature, and involve déjà vu's or ictal autoscopia (Elliott et al., 2009). In the case of epilepsy, these phenomena are rarely ever prolonged without being provoked by new seizures.

Schankin et al. (2013) report on a number of individuals that show resemblance to our cases and who are debilitated by the experience of visual snow accompanied by other visual symptoms such as excessive perception of floaters, afterimages, and flashes. They propose this is a new syndrome altogether which they named the 'visual snow syndrome'. It is

explicitly mentioned that the symptoms are not necessarily related to drug use. Also, the majority of the cases reported by Schankin et al. (2013) have a history of migraine.

Despite the many differences, there may be a common pathway between seemingly diverse conditions that are associated with visual hallucinations (Manford and Andermann, 1998; Teeple et al., 2009). Though our cases do not seem to meet the criteria for these other conditions, they cannot be discarded as possible underlying factors for the experienced visual symptoms either. Some of these disorders may be excluded with neurological and ophthalmologic tests, such as a multifocal electroretinogram, EEG or MRI. However, these tests are not failsafe as EEG and MRI appear to be normal in e.g. migraineurs (Liu et al., 1995. Because our diagnosis of HPPD relied mainly on the psychiatric diagnosis and attribution of the symptomatology to drugs by the patients themselves, a possible overlap is investigated by comparing symptoms of some of the well-known visual disorders and the symptoms of our 31 HPPD cases (Table 2).

Place *Table 2* here

6. Serotonin neurotransmission in the visual system and HPPD

Since low-level visual processing could be involved in the etiology of HPPD and the involvement of serotonergic drugs, the role of serotonergic neurotransmission in low level-visual processing is investigated. Consequently, it is also of interest how long-term changes are induced in the functioning of lower visual areas.

6.1 Serotonergic neurotransmission in lower visual areas

The 5-HT_{2A} receptor is abundantly expressed, especially in layers III and V of the brain's neocortex (Nichols, 2004). Agonism at 5-HT_{2A} receptors can both facilitate and inhibit the firing of neurons, depending on the type of neuron on which the receptor is present (Nichols, 2004; Paspalas and Papadopoulos, 2001). Post-mortem studies have shown that a high density of 5-HT_2 receptors is present in human V1 (Zilles et al., 2002). Whether these receptors are also present in the LGN is unclear; the 5-HT_{2A} receptor was detected in the LGN of rats (Cornea-Hebert et al., 1999), but appears absent in macaques that did display high expression of 5-HT_{2A} in V1 and V2 (Watakabe et al., 2009). Thus, it appears that a major target for hallucinogenic drugs is present in areas of low-level visual processing. These receptors receive serotonergic input from axons of the raphe nuclei that are known to innervate V1 (Watakabe et al., 2009), though the function of 5-HT_{2A} receptors in low-level visual processing remains largely unexplored. Nonetheless, Watakabe et al. (2009) have shown that 5-HT_{2A} agonism can both suppress strong responses and facilitate weak neuronal responses in primate V1. Therefore, it seems possible that the acute effects of hallucinogens and MDMA are mediated by interaction with these receptors in lower visual areas.

6.2 The proposed mechanism of HPPD

A type of neuron that is possibly involved in the etiology of HPPD is the inhibitory cortical interneuron, which expresses 5-HT_{2A} receptors and releases GABA upon activation. Abraham and Aldridge (1993) proposed that damage to this type of neuron may be involved

in HPPD. Symptoms such as afterimages and halos may be explained by a lack of inhibition; (lateral) inhibitory mechanisms are important to suppress neuronal responses when the stimulus is no longer present and a lack of lateral inhibition may decrease the ability to process edges and thereby result in the perception of halos. Symptoms such as visual snow during adaptation to darkness could be a cue that a drop in signal to noise ratio plays a role, as a lack of inhibitory input causes internal noise to be passed on as a signal that would be suppressed under normal circumstances (Abraham, 1983). Abraham and Wolf (1988) found that subjects with previous exposure to LSD perceived a flickering light as continuously 'on' at a lower flicker frequency than controls. The role of GABA-releasing interneurons can also be inferred from the observation that GABA-R agonists like benzodiazepines often alleviate symptoms of HPPD patients (Halpern and Pope, 2003).

A broader view of a misbalance between excitatory and inhibitory input in the visual system of HPPD sufferers offers a more open approach to studying the etiology of HPPD. For example, computational studies by Kilpatrick and Bard Ermentrout (2012) suggest that merely increasing the excitatory input into V1 can result in HPPD symptoms such as halos. These computational studies also suggest that an increase of both excitatory and inhibitory input, while maintaining an equal ratio, could result in more complex symptoms such as afterimages (Kilpatrick and Bard Ermentrout, 2012).

Using the tilt after-effect as a measure for lateral inhibition between orientation-selective neurons, Murray et al (2012) found a significantly larger tilt after-effect for MDMA users adapting to real contour stimuli, whereas the response to illusory contours was not so much affected. This was taken as a cue that lateral inhibition is affected in primary visual cortex V1, but not so much in V2 where illusory contours are processed. Finally, increased excitability of LGN and visual cortex by visual stimuli was found in an fMRI study with long abstinent MDMA users (Bauernfeind et al., 2011).

The fact that the excitatory visual signal is present for a long period of time in HPPD seems to oppose elementary hallucinations, resulting from applying pressure to the eyeball (phosphenes), which causes similar nonlinear dynamic interactions between excitatory and

inhibitory cortical neurons as described by Kilpatrick and Bard Ermentrout (2012), but of short-term duration (Billock and Tsou, 2012).

Concluding, it is impossible to determine whether HPPD-like effects occur as a result of lacking inhibition, an increase in excitation, or a combination of both. HPPD-like effects may lead to increased excitation and decreased ability to respond to 'on' and 'off' switching stimuli. Therefore, it may be safer to speak of a misbalance between inhibitory and excitatory input in visual processing, regardless whether damage to 5-HT_{2A} receptors-expressing inhibitory interneurons occurs.

6.3 Neurophysiological changes induced by hallucinogenic drugs

Experimental results in animals suggest that MDMA is potentially neurotoxic to axons projecting from the raphe nuclei (Green et al., 2003). Although there is still some debate as to whether this neurotoxicity occurs in human users, several brain imaging studies have shown drastically reduced SERT levels in heavy ecstasy users (Kish et al., 2010; McCann et al., 2005; Schouw et al., 2012). Imaging studies with positron emission tomography (PET) showed reduced cerebral 5-HT_{2A} receptor densities in recent MDMA users, whereas expression was increased in ex-MDMA users and in rats 30 days after administration of MDMA (Reneman et al., 2002). This difference in short-term versus long-term effects may be related to the delayed onset of symptoms in some HPPD patients.

While MDMA can induce long-term changes in serotonergic neurotransmission, this remains largely unstudied for classic hallucinogens. Administration of a single dose of 1 mg/kg LSD to rats did not affect serotonin 1A, 2A, and 2C receptor expression in various brain areas, but did increase expression of several genes associated with synaptic plasticity and glutamate signaling (Nichols and Sanders-Bush, 2002). This may suggest an actual strengthening of excitatory synapses instead of a decrease in inhibition. Ketamine also increases transcription of several genes involved in synaptic plasticity, among which Arc and the glutamate-AMPA-receptor-1 (GluR1) in the PFC (Duman et al., 2012). Moreover, it has been shown that ketamine also affects the visual cortex (Yu et al., 2012).

Cannabis (delta-9-tetrahydrocannabinol) is another drug that relies primarily on interaction with serotonergic targets for its effects. Notably, a (comparatively small) group of users ascribe the development of visual symptoms to cannabis use (Carhart-Harris and Nutt, 2010) and a benign, time-limited kind of visual disturbance has been reported by abstinent users (Lerner et al., 2011). Recent studies indicate that CB_1 receptor agonists modulate signal transmission from LGN to visual cortex (Dasilva et al., 2012) and that extensive cannabis use affects expression of the CB_1 receptor (Rotter et al., 2013). Also, CB_1 receptors seem to serve a function in the development of GABA-ergic neurons in the visual cortex (Pinto et al., 2010; Yoneda et al., 2013). Additionally, the cannabinoid system has various interactions with the serotonin system through actions on the raphe nuclei (Mendiguren and Pineda, 2009) and may modulate the main target for classical hallucinogens by upregulating 5-HT_{2A} receptor expression (Franklin and Carrasco, 2013; Hill et al., 2006).

These different hypotheses are schematically illustrated in figure 4, which shows an inhibitory interneuron with potential sites for drugs to cause HPPD.

Place Figure 4 here

6.4 Co-morbidity with other psychiatric conditions

The high comorbidity with other conditions such as anxiety, panic, decreased attention, and depersonalization/derealization (DP/DR) in our cases forces us to consider the relationship of these conditions to visual perception.

A recent study has shown that anxiety modulates contrast sensitivity in low-level visual processing (Ferneyhough et al., 2013). It is therefore possible that anxiety plays a modulating role. Since benzodiazepines are used to dampen anxiety and panic (Bandelow et al., 2002), the beneficial effects of these drugs on HPPD may also be used as an argument in favor of anxiety playing a role in HPPD symptoms. Treatment with clonidine, an agent that dampens sympathetic stimulation and which is prescribed for anxiety, also showed beneficial effects for treating HPPD symptoms in a pilot study (Lerner et al., 2000). The way in which anxiety affects visual processing may be related to attentional mechanisms. Attention modulates neural responses in low-level visual areas such as V1 (Roelfsema et al., 1998) and it is common that HPPD patients find some relief after they learn to distract their attention from the visual symptoms. However, no clues were found on the relationship between anxiety and the HPPD symptoms in literature.

DP/DR symptoms are also frequently mentioned by our cases presented in *Table 1*. Sierra et al. (2012) report that in some individuals with DP/DR symptoms and a high level of anxiety, the symptoms are accompanied by visual phenomena such as flashes and 'hallucinatory-like experiences'. Additional evidence for a relationship and possible overlap between HPPD and DP/DR was provided by a survey among individuals with depersonalization syndrome. Interestingly, this survey found that hallucinogens, cannabis, and ecstasy were the most commonly mentioned drugs of cause among 196 participants that reported their symptoms to be drug-initiated (Simeon et al., 2009). The high co-morbidity of psychiatric conditions illustrates that HPPD is probably not limited to the visual system and multiple brain areas may be involved.

7. Discussion

Recent studies suggest that visual disturbances occur with some regularity resulting from the use of hallucinogenic drugs and MDMA. These disturbances may be accompanied by severe incapacitation, affecting everyday functioning of these users. A group of lay users ascribed symptoms of abnormal visual perceptions to the preceding use of drugs belonging mainly to the serotonergic class (Baggott et al., 2011; Carhart-Harris and Nutt, 2010). The present review proposes that serotonergic neurotransmission and the 5-HT_{2A} receptor, which are involved in low-level visual processing, are possible targets for both classical hallucinogens and MDMA to induce long-term visual changes, such as HPPD.

The effects of medications, like the worsening of HPPD symptoms by 5-HT_2 antagonists, the relief by benzodiazepines, and decreased critical flicker frequency in LSD users seem to be in accordance with a hypothesis of decreased inhibition in low-level visual processing. Therefore, the 5-HT_{2A}-R expressing inhibitory interneuron hypothesis would seem a promising target for further investigation. For instance, future research may examine 5-HT_{2A} receptor densities in visual areas of HPPD patients with PET, or investigate with neurophysiological techniques whether increased excitability of the visual system is especially pronounced among HPPD patients.

The working mechanism of cannabinoids or ketamine does not primarily rely on serotonergic neurotransmission, though these drugs were mentioned as a cause for HPPD symptoms by some patients in our (Table 1) and other samples (Carhart-Harris and Nutt, 2010; Gaillard and Borruat, 2003). From this review, it seems that these substances provide a relatively small contribution to the total amount of individuals with HPPD complaints. Nevertheless, it is important to realize that perceptual processing in the long-term could also be affected by alternative neurobiological routes and that even if these drugs do not cause HPPD by themselves, they may play a role in sensitizing an individual to the development of visual complaints. In fact, the use of multiple drugs may be at the basis of symptom development. Extensive cannabis use may sensitize the individual to develop HPPD after the use of LSD for example.

Some users reported to be incapacitated to some extent by their symptoms (Baggott et al., 2011; Carhart-Harris and Nutt, 2010), whereas a large group of users appeared to experience symptoms without impairment, and the majority of drug users did not develop any symptoms. This is an intriguing finding. Factors such as genetic polymorphisms in SERT, CYP2D6, and COMT genes have been shown to play a role in the development of clinical symptoms and decreased cognitive functioning in MDMA users (Cuyas et al., 2011; Rietjens et al., 2012). However, these genes have not yet been studied in relation to hallucinogenic drug use or abnormal perceptual symptoms. Other factors that may influence the development of HPPD symptoms and their severity could be environmental, e.g. the conditions under which the drug was taken. For instance, prolonged sleeplessness is often mentioned by recreational polydrug users and influences the expression of 5-HT_{2A} receptors (Elmenhorst et al., 2012). Another knowledge gap relates to the uncontrolled setting in which drugs were used and therefore, the unknown quality or quantity of the drug that was consumed. Street ecstasy may contain a large variety of substances other than MDMA (Brunt et al., 2012). Environmental conditions can easily be controlled in a clinical setting and may therefore provide an explanation for the discrepancy in prevalence rates of HPPD between controlled clinical settings and lay user environments (Nichols, 2004; Studerus et al., 2012).

When comparing the symptoms of HPPD in literature and our new cases with other possible underlying conditions, it seems unlikely that the phenomena were caused by significant factors outside drug use. However, without appropriate neurological tests this cannot be excluded. For example, our subjects reported visual symptoms that are included in the DSM IV-TR, but also a large variety of other symptoms such as eye floaters, tinnitus, oversensitivity to sound, sensations in the head, depersonalization, derealization, anxiety, and depression. This is a serious concern for proper diagnosis and the exclusion of other conditions. On the other hand, the definition of HPPD as described in the DSM IV-TR could be too limited.

8. Conclusion

HPPD is a rare perceptual disorder, but the burden of disease for those affected can be substantial. A misbalance of inhibitory/excitatory signaling in low-level visual processing may be involved, with a likely role for serotonergic neurotransmission. Therefore, cortical 5-HT_{2A} expressing inhibitory interneurons provide an interesting subject for future study. HPPD is a condition that is not limited to LSD and other classical hallucinogens. This review also implicates ecstasy (MDMA) as causative agent for HPPD-like symptoms. Despite the fact that HPPD doesn't pose a large public health threat, it remains an intriguing phenomenon that deserves more scientific study, also from the perspective of improvement in the understanding of the visual system.

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11. Tables and figure legends

Fig. 1: Geometric hallucinations: the patterns seem to move along with eye movements (Reprinted by permission from Macmillan Publishers Ltd: Nature. Billock, 2010. Neuroscience: Patterns from the Brain. Nature 468, 630-631, Copyright 2010).

Fig. 2: An example of trailing, whereby a moving object is followed by a series of stationary images along its trajectory (Dubois and VanRullen, 2011) Reprinted by permission from Dubois according to the Creative Commons Attribution License).

Fig. 3: Afterimages, or palinopsia, differ from trailing in that moving objects are not followed by a discrete series of images but a moving object would rather leave a continuous smear (Reprinted from Optometry, **81**(8), Abert B, Ilsen PF, Palinopsia, 394-404, Copyright (2010), with permission from Elsevier).

Fig. 4: A schematic representation of an inhibitory interneuron as it may exist in low visual areas like V1 and the LGN. Sites where drugs can induce long-term changes are depicted with geometric shapes (▲, ●, ♦, ■). The scheme is an evolved adaption of the damaged interneuron hypothesis as initially proposed by Abraham and Aldridge (1993). The excitatory signal is transmitted by glutamate via AMPA receptors (AMPA-R) and is modulated by 5-HT_{2A} receptor-expressing cortical interneurons that inhibit neuronal firing through the release of GABA and subsequent activation of GABA receptors (GABA-R). Inhibitory mechanisms are important to suppress neuronal responses when the stimulus is no longer present and a lack of inhibition, due to damage to these interneurons, may therefore explain prolonged false visual representations of reality. An alternative to the damaged interneuron hypothesis is an increase in strength of excitatory synapses. LSD (▲) and ketamine (●) have been shown to increase transcription of AMPA receptors. The resulting strengthening of excitatory synapses modulates the strength of the visual signal. MDMA research suggests its

neurotoxicity to serotonergic axons. MDMA-induced (♦) damage to serotonergic axons may lead to decreased serotonin release onto 5-HT_{2A} receptors, thereby decreasing the baseline level of inhibition and indirectly reinforcing visual signals. Delta-9-tetrahydrocannabinol (■) plays a role through its effects on the development of GABA-ergic neurons in V1, by altering serotonergic signaling, or by modulating the excitatory signal.

Table 1. New XTC-related cases of HPPD obtained from a psychiatric consultancy service in the Netherlands.

	PERCEPTUAL SYMPTOMS															PSYCHIATRIC								USED SUBSTANCES															
	Visual												Auditory		Sensory									Before symptoms[a]		Life-time[b]													
	visual snow	specks	flashes	floaters	afterimages or stripes	illusory movement	halos	geometric shapes	blurred vision	changed color perception	disturbed depth perception	harder to focus	tinnitus	oversensitivity to sound	unnatural sensations head	tingling in extremeties	anxiety and/or panic	decreased attention	sleep problems	fatigue	depersonalization	derealization	decreased memory	depression	bad trip (Y/N)	alcohol	cannabis	ecstasy (MDMA)	psilocybin mushrooms	LSD	phenetylamines	NMDA antagonists	cocaine	amfetamines	GHB	opioids
SV						o											o	o			o	o		o	CAN		E	D	M					L				
RF	o									o		o	o	o	o	o	o			o		o		o	CAN, ALC		M	E										
JS	o			o	o	o	o			o	o				o		o			o	o	o		o	LSD	Y		D	E					L				
RT	o			o								o													LSD		M	M	M		L	L	L		L			
TS			o	o	o									o											LSD			M										
LM	o		o	o						o		o		o			o				o	o	o		MDMA, BENZO	Y	M	D	L					L				
TA1	o		o	o	o	o				o				o	o		o			o				o	MUSH					L								
LB					o	o	o								o			o				o	o	o	MUSH, CAN, ALC		E	L		L									
CO	o			o	o	o						o	o		o		o	o	o		o		o		n.s.			M	E	L					L	E	M		
DM	o		o				o										o								n.s.		E	M	E					L	M				
EB			o	o		o					o		o		o		o	o		o		o	o	o	n.s.		D	D	D					D	E		D	
JB	o												o				o								n.s.			D	M									
OH			o	o	o								o		o			o							n.s.		M		M					L	L			
BH	o		o			o						o						o					o		XTC	Y	E	D	M	L				M	M	L		
BR						o			o				o				o				o	o	o		XTC			D	E	M	L	M	M	M	M	M		
BV	o			o	o															o					XTC			M	L									
CA				o						o		o			o		o	o	o		o	o			XTC		L	E	M					L	L			
IG	o			o													o						o		XTC				E	L	L							
JG					o							o					o			o					XTC		M	L										
KH			o	o											o			o							XTC		M	M	L									
MH			o							o					o	o	o				o			o	XTC	Y		M	E					M				
PB			o	o	o	o	o				o				o	o	o		o				o	o	XTC		E	D	E					L		L		
SH	o	o		o	o												o				o	o		o	XTC				E									
SM	o			o	o	o		o				o					o					o			XTC			L	E	L				M	L	M		
TA2	o		o	o	o										o				o			o	o	o	XTC		L	M	M			M		M	M			
RB	o		o	o		o						o	o		o		o					o	o		XTC		M	E	L									
JE	o			o	o					o					o						o				XTC		E	L	L									
AM	o		o			o	o						o			o	o							o	XTC, ALC	Y		D	M	L				L				
MP	o		o	o		o					o						o							o	XTC, ALC	Y	E	L	M									
NS	o		o	o	o		o			o							o	o	o					o	XTC, ALC	Y	D		E									
AL	o			o	o		o										o	o			o		o		XTC, ALC, CAN, AMP		E	E	E			M		M				
Total (%)	61	3	48	68	48	42	23	3	3	26	13	29	26	13	45	13	71	32	19	19	32	39	35	42															

[a] Drugs that were used on the occasion before symptoms were present. Most of these occasions took place within one week before symptom onset whereas in few occasions this period was longer. When the onset of symptoms could not be ascribed to a specific occasion, this is indicated in the tabe as not specificied (n.s.).

[b] Histories of drug exposure are categorized as low (L), moderate (M), or extensive (E), an extended period of daily use (longer than 1 month) of a certain drug is indicated with a D.

L = less than 10 lifetime exposures for XTC, amphetamines, psilocybin mushrooms, LSD, phenetylamines, NMDA antagonists and cannabis OR less than 3 units per occasion of alcohol use.

M = 10 to 50 lifetime exposures for XTC, amphetamines, psilocybin mushrooms, LSD, phenetylamines, NMDA antagonists, and cannabis OR 3 to 10 units per occasion of alcohol use on a regular basis.

E = more than 50 lifetime exposures to XTC, amphetamines, psilocybin mushrooms, LSD, phenetylamines, NMDA antagonists, and cannabis OR more than 10 units per occasion of alcohol use on a regular basis.

n.s. = not specified. A large group of users report symptoms after an extended period of intensive drug use and are unable to link symptom development to a specific occasion.

Table 2. Differential diagnoses and their visual symptoms compared to HPPD and the cases described within this review.

	Main visual symptoms	Main co-occurring symptoms	Triggered by	References
HPPD cases described within this review	Episodic or constant visual snow, geometric hallucinations, floaters, flashes, afterimages, illusory movements, altered colour perception	Unnatural feeling of the head, depersonalization, derealization, anxiety and depression (mainly secondary)	Drug use in week before symptom development (mainly ecstasy and serotonergic drugs)	(this review)
HPPD	Geometric hallucinations, illusory movements, flashes of colour, altered colour perception	Not specified	LSD use	(Abraham, 1983)
Migraine with Aura	Aura typically lasts < 1 hour consisting of flickering light, zig-zag lines starting in the centre of the visual field progressing to the periphery, scotoma	Visual symptoms almost always precede migraine headaches but aura may occur without headache, sensory aura with affecting hands and face progressing over the body	Migraine episode (usually)	(Russell and Olesen, 1996)
Persistent migraine aura	Constant symptoms such as visual snow, flashes, light spots	More than 10 headache episodes per month		(Chen et al., 2011)

Temporal-occipital lobe epilepsy	Déjà vu, autoscopia	Anxiety, psychosis	Epileptic seizures	(Elliott et al., 2009)
Occipital lobe epilepsy	Bright coloured spots, circles, and balls lasting for 5-30 seconds and blindness	Often followed by post-ictal headache and/or by secondary tonic clonic convulsions in 16 of 18 in this study	Epileptic seizures/ headache	(Panayiotopoulos, 1999)
Visual snow	Visual snow plus an additional symptom such as floaters, afterimages or flashes	Not specified	Distinct from migraine with aura but high prevalence of migraine history and not related to drug use	(Schankin et al., 2013)

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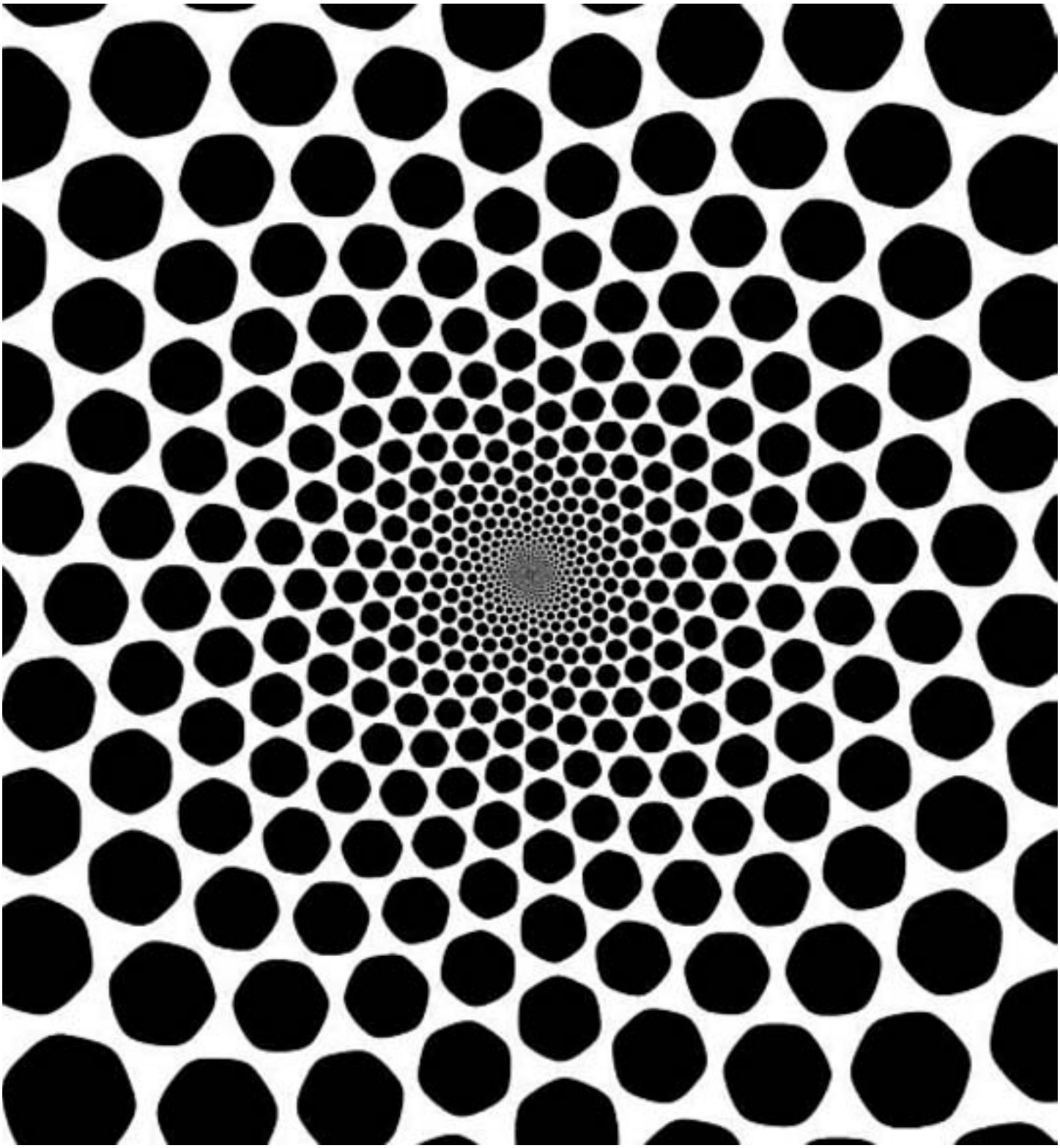

Figure(s)

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